Serial No.: 09/341,119
Attorney Docket. No.: P63712US0

REMARKS

Claims 38-60 are presented, hereby, in place of claims 14-37.

Applicants wish to thank the Examiner for correcting the numbering of claims found in the Amendment filed 14 August 2001, as explained in the Office Action. It is also noted that, by the Supplemental Amendment filed November 21, 2001, the second claim numbered "36" was replaced by new claim 37.

Claim 38, presented hereby, corresponds to claim 14 amended by changing "a mixture having different species of nucleic acids in addition to circular nucleic acids" to read ––a *bacterial crude lysate* mixture–– (*emphasis added*), as recited in original claim 4. Claims 39-60 correspond to claims 15, 16, and 18-37, respectively.

Claim 14 is amended in this fashion (as claim 38) to emphasize a feature of the invneiton that reflects a crucial advancement over the prior art, i.e., taking a bacterial *crude* lysate and applying it to a solid, silica-containing matrix *without any pre-purification steps.* The crude lysate is not purified in any way but, rather, it is applied *as the crude lysate* directly to the silica-containing matrix.

Therefore, by applying the *crude* lysate to the matrix, as in original claim 4, the present claims exclude from claim scope those procedures for separating and/or isolating circular nucleic acids from a bacterial crude lysate sample in which the crude lysate sample is *first* subjected to purification steps before being applied to a silica containing-matrix.

As to the word "crude," Applicants are aware that the use of the word was considered

indefinite in the Office Action mailed February 14, 2001. However, the phrase "bacterial crude lysate" is not indefinite, as its meaning would not have been confusing to one skilled in the art, in particularly in view of the context of use in the invention as described and claimed in the application; that is, it refers simply to the crude mixture obtained after lysing is performed, without any purification of the mixture.

The correct test for indefinite claim language is whether one of ordinary skill in the art would be confused as to the meaning of subject matter defined by the language at issue. *In re Kroekel*, 183 USPQ 610 (CCPA 1974). In applying this test, limitations from the specification cannot be read into the claims; *however*, words in the specification are properly used *during prosecution* as an aid in interpret *existing* claim limitations. *In re Donaldson Co. Inc.*, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994). Moreover, the Examiner's definition of a claim limitation cannot conflict with the definition given in the specification. *In re Zletz,* 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). The Examiner must use the specification definition in construing the claims for comparison with the prior art.

> When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.

Zletz, 13 USPQ2d at 1322. Applying the aforesaid standards to the present facts demonstrates that the language at issue satisfies the requirements of 35 USC 112, ¶2, i.e., the language is not indefinite.

Claims were rejected under 35 USC 112, ¶1, for alleged lack of enablement. Reconsideration is requested.

The presently claimed invention provides, inter alia, a method for separating circular nucleic acids, particularly plasmids. The separation is performed, under alkaline conditions at a pH > 8 and in the presence of at least one chaotropic substance, by treating the DNA with a silica-containing solid matrix . As a result, the circular DNA binds to the silica material in the matrix. The separation procedure in accordance with the presently claimed invention is a simple process and it increases the recovery of pure circular nucleic acids in comparison with the prior art methods, such as those of Marko and Little, of record.

According to the statement of rejection, the claims are overly broad with respect to performing the claimed method at "pH> 8 . . . in the presence of at least one chaotropic substance." It is alleged that enablement is not satisfied for using any chaotropic agent at any pH over 8 to separate circular DNA from RNA and linear DNA "in view of the highly unpredictable nature of the subject matter claimed." Gautsch (U.S. Patent No. 6,027,750), columns 13 and 14, Table 2, is said to demonstrate that binding plasmids to glass cannot be obtained "using certain chaotropic agents at pH 8.0." Boom (U.S. Patent No. 5,234,809), column 14, Example 5A is also relied on in the statement of rejection, in this respect. The statement of rejection also alleges that Example 2, at page 22, of the instant specification demonstrates that binding cannot occur at a pH above 12 under any conditions in accordance with the presently claimed invention and, so, "the claimed objective of preferential plasmid binding cannot be achieved under all of the conditions encompassed by the claims."

The statement of rejection contains clearly erroneous factual allegations and evidences failure to apply the correct standards for determining satisfaction of the requirements for enablement under §112, ¶1.

First of all, the PTO burden of establishing lack of enablement under §112, ¶1, is not satisfied by the allegation of unpredictability in the art. Even in an unpredictable area the PTO must advance reasons why a patent applicant's broad assertion of enablement is not true. *In re Bowen*, 181 USPQ 48 (CCPA 1974). In order to sustain a rejection for lack of enablement under §112, and shift the burden to a patent applicant, the PTO must advance *reasoning* inconsistent with enablement. *In re Sichert*, 196 USPQ 209 (CCPA 1977).

In the present case, the statement of rejection merely shows that all theoretically possible combinations of conditions within the scope of the present claims would not result in the claimed objective of selectively binding circular DNA. Such a showing does not establish lack of enablement. All it shows is that some *routine experimentation* is necessary to adjust conditions within the claim scope to obtain the claimed objective.

In fact, findings made in the instant Office Action, itself, show that only routine experimentation is necessary to adjust the pH level. According to the instant Office Action (page 6, ¶2), adjusting pH level to be result effective is an *obvious matter of routine optimization*.

Example 2 of the present specification is misscharacterized in the statement of rejection. Example 2 does not show binding cannot occur at pH 12 under *any* conditions; it only shows that binding at pH above 12 does not occur under *all* conditions. That is, using the conditions set forth

in Example 2, binding did not occur at pH above 12 and, so, *the claimed objective of preferential plasmid binding cannot be achieved under* certain specific *conditions encompassed by the claims*, not "all" conditions, as alleged in the statement of rejection. Claims need not be limited only to those working embodiments disclosed in the specification; working embodiments in the specification are not even required to satisfy enablement under §112, ¶1. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982).

An upper limit of the pH need not be recited in the claims to satisfy the requirements of enablement. The issue presented concerns how to practice the invention, which is the function of the specification, not the claims. *In re Roberts*, 176 USPQ 313, 315 (CCPA 1973).

Applicants also observe that Boom, relied on in the statement of rejection, does not even mention any pH in Table A 5.1 of Example A5.

With respect to covering chaotropic agents, generically, the statement of rejection relies on concerns that not all chaotropic agents would work in the presently claimed invention. That not all chaotropic agents would work fails to establish lack of enablement under §112, ¶1. The "use of materials which might prevent achievement of the [claim] objective . . . can hardly be said to be within the scope of the claims." *In re Geerdes*, 180 USPQ 789, 793 (CCPA 1974). Section 112 enablement is satisfied when generic claims cover thousands of end products, some of which may not be operative (i.e., may not work for the stated purpose of the claimed invention). *Atlas Powder v. E. I. duPont de Nemours*, 224 USPQ 409 (Fed. Cir. 1984). The mere presence of some non-

working embodiments within a generic claim does not justify a rejection for lack of enablement under §112, first paragraph.

> As we have said before, it is almost always possible to so construe a claim as to have it read on non-working embodiments, In re Cook, 58 CCPA 1049, 1054, 439 F.2d 730, 734, 169 USPQ 298, 301 (1971), but the alternative of requiring an applicant to be so specific in his claims "as to exclude materials known to be inoperative . . . would result in claims which would fail to comply with 35 U.S.C 112, second paragraph, because they would be so detailed as to obscure, rather than to particularly point out and distinctly claim, the invention. In re Meyers, 56 CCPA 1129, 410 F.2d 420, 161 USPQ 668 (1969), quoted with approval in In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

In re Smythe, 178 USPQ 279, 286 (CCPA 1973)(*emphasis in original*).

Accordingly, the enablement under 35 USC 112, ¶1, is satisfied in accordance with the presently claimed invention.

Claims 14-29, 21-24, 27-30, and 34 were rejected under 35 USC 103(a) based on the combined teachings of Little and Marko. Claims 14-24 and 27-34 were rejected under 35 USC 103(a) based on the combined teachings of Little, Marko, Smith and Segel. Claims 25, 26, and 35-37 were rejected under 35 USC 103(a) based on the combined teachings of Bastian (either the U.S. patent or the corresponding published International application) and Segel. Reconsideration is requested with respect to the aforesaid rejections.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior

art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

In the context of a rejection for obviousness under §103, the "*Examiner* bears [both] the initial burden . . . of presenting a *prima facie* case of unpatentability" and "the ultimate burden of persuasion on the issue." *In re Oetiker*, 24 USPQ 1443, 1444 and 1447 (Fed. Cir. 1992), *emphasis, added.*

The "evidence upon which the examiner relies must clearly indicate that a worker of routine skill in this art would view the claimed invention as being obvious." *Ex parte Wolters*, 214 USPQ 735, 736 (BPA&I 1982). "It is facts which must support the legal conclusion of obviousness." *Ex parte Crissy*, 201 USPQ 689, 695 (POBdApp 1976).

> The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

In re Warner, 154 USPQ 173, 178 (CCPA 1967) (*emphasis in original*). An argument by the USPTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When the

> USPTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears *in the reference*. . . . The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. . . . [S]uch a retrospective view of inherency is

> not a substitute for some teaching or suggestion supporting an obviousness rejection.

28 USPQ2d at 1557, *emphasis added.*

When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not suggest . . . modification of the . . . [prior art], or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

"The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art *would lead* that individual to combine the relevant references. . . . Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so." *Ex parte Obukowicz*, 27 USPQ 1063, 1065 (BPA&I 1992)(*emphasis, added*).

As explained by the Board in the decision *Ex parte Levengood*, 28 USPQ2d 1300, 1300-01 (BPA&I 1993)(*emphasis in original*):

> In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,[1] preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention [*citations, omitted*].

The fact that all elements of a claimed invention are known does not, by itself, make the combination obvious. *Ex parte Clapp*, 227 USPQ 972 (BPA&I 1985). To support a rejection for obviousness based on the combination of separate prior art teachings, the USPTO "must identify

specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998).

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986).

To reject claims for obviousness under §103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

> . . . that it would also have been obvious *how* this [modification] could be achieved . . . . Obviousness . . . must not be judged by hindsight, and a "little modification" can be a most unobvious one.

In re Irani, 166 USPQ 24, 27 (CCPA 1970) (*emphasis in original*).

The statement of rejection takes the point of view that the determination of a suitable pH range for practice of the process disclosed by Little and Marko would have been obvious, *per se*, as a matter of routine optimization. Interestingly, this directly contradicts the argument made in support of the alleged lack of enablement for determining pH in accordance with the present claims.

In any event, per se obviousness based on routine optimization has long since been discredited. "Reliance on *per se* rules of obviousness is legally incorrect and must cease." *In re*

Ochai, 37 USPQ2d 1127, 1129 (Fed. Cir. 1995). If the prior art fails to disclose a rationale for varying parameters to be result effective, it can not have been obvious to choose the claimed parameter. *In re Antonie*, 195 USPQ 6 (CCPA 1977). Obviousness cannot be based on speculation.

> The examiner should be aware that "deeming" does not discharge him from the burden of providing the requisite factual basis and establishing the requisite motivation to support the conclusion of obviousness. . . . The examiner's reference to unidentified phantom prior art techniques . . . falls short of the mark.

Ex parte Stern, 13 USPQ2d 1379, 1382 (BPA&I 1989).

> Whether the changes form the prior art are "minor", as . . . [patent challenger] argues, the changes must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the . . . [claimed] method and device.

Northern Telecom, Inc. v. Datapoint Corporation, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990).

Differences between the claimed structure and the prior art structure do not amount to "an obvious design choice," when "the different structures . . . achieve different purposes." *In re Gal*, 25 USPQ2d 1076, 1078 (Fed. Cir. 1992).

Where the *optimization* of a claim variable was not recognized in the art as effecting the claimed result, the result is unobvious. *In re Antonie*, 195 USPQ 6, 8 (CCPA 1977). That a difference with the prior art amounts to an alleged "optimal condition . . . is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

Moreover, routine optimization is not involved. As can be seen from the Marko citation Marko et al. discloses a two step process to isolate pure plasmid DNA. This can clearly be seen from the whole document. See for example introduction on page 382.

> In this report, we describe an extension of an earlier analytical procedure 94), which allows isolation of a highly purified plasmid DNA in large quantities without the use of cesium chloride banding, ribonuclease treatment, phenol extraction, or dialysis. Extraction of lysozyme-treated bacterial cells under defined alkaline conditions selectively denatures chromosomal DNA but not CCC-plasmid DNA. When the crude alkaline extract is neutralized, high-molecular-weight chromosomal DNA aggregates to form an insoluble network; high-molecular-weight RNA and protein-SDS complexes are likewise rendered insoluble by the simultaneous addition of high concentration of salt. After removal of insoluble material by centrifugation, soluble plasmid DNA is bound to glass powder (5-7) and washed extensively with sodium perchlorate to remove remaining contaminants. Finally, highly purified DNA is recovered in high yield by elution with a low-ionic-strength buffer.

Moreover, from the detailed description for the isolation of Plasmid pBR322 DNA from Escherichia coli it clearly can be seen that this procedure comprises six steps including tw of alkali treatment (page 383):

1. Growth of cells
2. Lysis and first alkali treatment
3. Second alkali treatment to remove residual DNA (optional)
4. 5 M Lithium chloride treatment to remove residual ribosomal RNA and single stranded DNA.
5. Proteinase K digestion (optional)
6. Final purification by adsorption to glass powder

Attention is respectfully referred to step 6. This step is the final purification step of the Marko procedure, to achieve pure plasmid DNA. Neglecting the optional steps (3 and 5) and the trivial first step, the Marko citations results in at least in a 3 step procedure.

In other words, Marko et al. do need pretreatment steps before binding the plasmid DNA onto the glass powder.

In contrast to Marko the presently claimed invention provides a method for plasmid DNA isolation form a crude bacterial lysate. This is achieved by the use of new buffer compositions which allow to selectively bind the plasmid DNA but not the chromosomal DNA on to a silica material.

The statement of rejection argues that the skilled person in the art would only have to determine the best suitable pH in the Marko procedure to arrive at the pure plasmid DNA, which can be isolated by the process of the present invention neglecting that Marko needs (a) pre-purification step(s) to extract chromosomal DNA which would possible bind also in an the silica surface in step 6.

On the contrary, Marko does not disclose any teaching with regard to the pH value because he was not faced in the last step to selectively bind plasmid DNA and not chromosomal DNA because there was no chromosomal DNA present in the mixture after Marko's pre-purification measurements. Similar to Marko et al., Littlestarts from a pre-purified DNA.

It is submitted that the method of Little is starting with a pre-purified DNA (for example disclosed in U.S. Patent No. 5,075,430 at col. 7, lines 19-30 and col. 8, lines 15-26). Little disclosed the following purification process:

One sample of DNA was prepared from 10 ml of overnight cultures using Triton-lysozyme lysis, followed by centrifugation of the chromosomal-membrane pellet. The supernatant was then precipitated with ethanol and dried.

In a second sample of DNA prepared from 10 ml of overnight cultures, the cells were lysed using SDS/NaOH. The mixture was then adjusted to pH 5 with a potassium acetate and centrifuged to sediment most of the chromosomal DNA along with some protein. The resulting supernatant was precipitated once with isopropanol and dried.

Three different plasmids, pBR 322, path and pRSVcat were prepared from 10 ml cultures of E. Coli HB101 cells using either the SDS/NaOH method or the rapid boiling method. Crude DNA was then purified on Celite following the procedures described hereinabove. Aliquots of the eluted purified DNA were digested with restriction endonucleases following known procedures and their concentrations estimated on an 1% agarose gel. This is in contrast to the presently claimed invention wherein new buffer compositions were used which allow to selectively bind the plasmid DNA but not the chromosomal DNA on to a silica material.

The statement of rejection stated the point that Little, at col. 3, lines 44-48 discloses that in a high concentration of chaotropic agent the silica-containing diatomaceous earth used therein preferentially binds larger DNA over RNA and the small DNA linkers.

This step of Little's procedure is required for agarose gels that can be dissolved readily in chaotropes, such that DNA bands from gels may also be recovered.

The Little invention is a process for the immobilization of pre-purified DNA onto diatomaceous earth in the presence of a chatropic agent. In contrast the present invention discloses a methods for plasmid DNA isolation from a crude bacterial lysate.

None of the references teaches or suggests that a binding step of circular nucleic acids under the conditions of claim 38 to silica material could be functional without any pre-purification steps. It is surprising that one single component can be directly purified from a crude mixture comprising chromosomal double stranded DNA, RNA and numerous other components, many of which are sticky. By the method of the invention, the daily routine work of a person skilled in the art working in the field of molecular cloning is improved significantly as explained above. Applicants continue to maintain that the statement of rejection relies on an "ex-post-facto" analysis, which is not allowed in making an obviousness determination under §103. *In re Deminski* 230 USPQ 313 (CCPA 1986).

Serial No.: 09/341,119
Attorney Docket. No.: P63712US0

Favorable action is requested.

Respectfully submitted,

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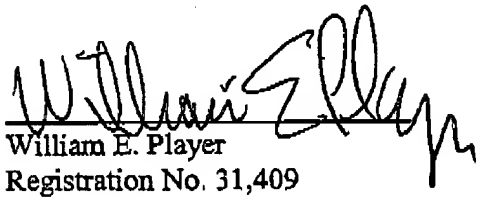
By 
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